REMARKS

The Examiner rejected claim 2 under 35 USC 112, second paragraph. Applicants respectfully traverse this rejection. Although claim 2 has been amended to delete the phrase "preferably mice of sound health", applicants have not amended the preamble of the claim to "a method for diagnosing septic shock conditions in an animal" as suggested by the Examiner. The method of claim 2 is a method for treating septic shock in an animal in which septic shock has been induced by the administration of LPS by administering curcumin prior to and after injection of LPS. Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claim 1 as being anticipated by Aggarwal (WO 97/09877). Applicants respectfully traverse this rejection.

The Examiner states that Aggarwal teaches in claim 1 a method of inhibiting the activation of the NF-kB transcription factor in an animal in need of such treatment comprising the step of administering to said animal a pharmacologically effective dose of curcumin, that claim 2 teaches that the animal is a human and that claim 3 defines that the human has a pathophysiological state selected from toxic/septic shock, graft vs. host reaction, radiation damage, atherosclerosis, AIDS, inflammation and cancer.

Applicants respectfully traverse this rejection.

Septic shock is a condition resulting from bacteremia or bacteria in the bloodstream. Septic shock effects different cell types such cell adhesion molecules like ICAM-1, VCAM-1 and E selectin and pro-inflammatory cytokines such as IL-1, TNF-α, NO, MIP-1α, CINC, etc. whose expression in turn may be upregulated or downregulated in septic shock conditions based on the intricate up or down regulation of the biochemical pathways and physiological mechanisms occurring at the cellular level.

To determine the effect on activation of NF-KB transcription factor

Aggarwal used transformed cell lines. Aggarwal shows inhibition of only the NF-kB transcription factor by curcumin in only ML-1a cell line (leukemic cells). See examples 6 and 7. This is a transformed cell line and there is no disclosure in Aggarwal that equates results obtained in neoplastic cells with results obtained in "normal" cells *in vivo*. There is no disclosure that ML-1a cells are a recognized model for septic shock. According to example 6, these cells were used because their response to NF-kB activation by various stimuli has been well characterized and the inventors found that curcumin activated NF-kB. The results of example 7 show that curcumin inhibits TNF-dependent NF-kB activation and that curcumin by itself did not activate NF-kB. The experiment also showed that TNF response was only inhibited when cells were pretreated with curcumin. Example 8 also shows that curcumin is a suppressor of NF-kB activation.

NF-kB is a transcription factor but is just one of many mediators for inflammation. In effect, Aggarwal teaches the inhibition of one transcription factor using curcumin and this is *in vitro*. Septic shock is a pathophysiological condition arising during due to systemic infection. It would therefore, be incorrect that a disclosure of use of curcumin to inhibit NF-kB transcription factor is a disclosure of the use of curcumin to treat septic shock.

Although reference is made in the specification and in the claims of Aggarwal to treating toxic/septic shock, no tests were carried out to study the effects of curcumin on septic shock-even on "normal" cell lines. In fact, on page 13 of Aggarwal it is stated that intervention in NF-kB activation may be (emphasis added) beneficial in suppressing toxic/septic, graft vs. host reactions, acute inflammatory reactions, HIV replication, acute phase response and radiation damage. This is just a supposition that curcumin may be beneficial in treating septic shock. There is no test data to support this statement nor is there any disclosure that would enable one of skill in the art to use curcumin to treat septic shock, which is one of the requirements that must be meet if a reference is properly cited under 35USC102(b).

Referring again to the sentence on page 13, it is noted that it is not limited

to just toxic/septic shock. It includes a list of conditions that are not linked by any common mechanism, toxic/septic shock can result from the presence of bacterial lipopolysaccharides (a foreign agent), graft vs. host reactions are immune responses not caused by the presence of bacteria, and acute inflammatory reactions can be caused by any number of conditions (e.g. allergens, insect stings). In addition, reference is made to HIV replication but there is no explanation of what this means (e.g. by what mechanism does curcumin effect HIV replication). There is no description of what an "acute phase response" is (acute phase response to what?). Radiation damage is a general term and there is no description of whether the radiation damage is internal or external and how curcumin could be used to treat it. The description in Aggarwal certainly does not enable claim 1 of this application.

In order for a reference to anticipate a claim the reference must disclose the invention and enable one skill in the art to practice the invention. On this basis, Aggarwal does not anticipate the invention.

There is no explanation in Aggarwal of how the dosage of 1mg to 100mg was obtained nor is there any evidence or explanation in Aggarwal that this dosage is effective to treat septic shock. The present application includes the dosage and the method by which it was determined that this dosage is effective.

Claim 1 of this application is a method for the treatment of septic shock in a subject by preventing neutrophil infiltration from blood vessels to the underlying tissues. There is no disclosure in Aggarwal that curcumin has any effect on neutrophils.

Therefore, since there is no enabling disclosure in Aggarwal of use of curcumin to treat septic shock, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 2-8 as being obvious over the combination of Aggawal, Majeed and Lai.

Applicants respectfully traverse this rejection.

As explained above Aggarwal does not teach the use of curcumin to treat septic shock. In addition, Aggarwal does not disclose or suggest treating septic shock in an animal in which septic shock has been induced by injection with LPS by administering curcumin prior to and after injection of LPS.

The Examiner states that Majeed teach that curcumin inhibits lipopolysaccharide induced nitrite production that is converted from nitric oxide and references the disclosure at col. 2, lines 32-33. However the disclosure at col. 2, lines 32-33 actually reads "Curcumin inhibited lipopolysaccharade (LPS) and interferon (INF) induced nitrite production by mouse peritoneal cells by more than 50% at 2.5-10 M." Firstly, this does not teach total inhibition, it teaches reduction in production. Secondly, the study was in mouse peritoneal cells (e.g. *in vitro* study).

This does not disclose or suggest the use of curcumin to treat septic shock *in vivo* in accordance with the conditions set out in claims 2-8. Furthermore, there is no disclosure in Majeed that would lead a person skilled in the art to have a reasonable expectation that curcumin can be used to treat septic shock.

Lai does not teach use of curcumin to treat septic shock. At col. 20, lines 59-60, Lai teaches that dithiocarbamate-containing compositions when activated, are advantagely effective as nitric oxide scavengers when employed with a thromboxane synthase inhibitor (e.g. curcumin) . The discussion of use of dithiocarbamate-containing compositions to treat septic shock is found in column 21 where it is stated that the dithiocarbamate containing compositions are employed in conjunction with the primary treating agent useful for treatment of septic shock. Curcumin is not included in the list of compounds in col. 21. Therefore, there is no disclosure or suggest in Lai that curcumin can be used to treat septic shock. The only mention of curcumin is its use as thrombaxane synthase inhibitor.

Therefore, since Lai is not a pertinent reference and no combination of Aggarwal and Majeed disclose or suggest the use of curcumin for treating

septic shock *in vivo* it is respectfully requested that this rejection be withdrawn.

Accordingly, applicants submit that this application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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2 (Amended). A method for the treatment of septic shock conditions in an animal wherein the [said] method comprises:

a) injecting intraperitoneally [the] a bacterial lipopolysaccharide (LPS) solution to an animal[, preferably mice of sound health,] to induce septic shock,

b) administering orally a pharmacologically effective dose of curcumin prior to and after the [said] injection of LPS,

c) observing every two to three hours reduction in severity of septic shock symptoms, the symptoms selected from shivering, lethargy, fever, watery eyes and diarrhea and monitoring the survival of [an] the animal [after] 8 hours after [of] administering the LPS injection, and

d) furthering probing the reduction in neutrophil infiltration from blood vessels to the underlying tissue by staining and microscopic examination for checking the extent of inflammation.